REVIEWS.

" La Lepra," by R. Chaussinand.

In writing this conveniently sized monograph of some two hundred pages, Dr. Chaussinand has done the same service to the French speaking world as Cochrane and Muir have done for the English speaking peoples. The voluminous classics of Hansen and Jeanselme are seldom read in these busy days, and even the moderately sized textbook of Rogers and Muir is not as widely read as it might be. Any author therefore who produces a concise, but adequate, account of leprosy, suited to the general practitioner in the tropics, is to be heartily congratulated. Dr. Chaussinand has done this work well, his writing is compellingly lucid in the best tradition of Laenner and Transzean. He shows due respect for authority, but his work is no mere copy; it bears the strong imprint of original observation and research.

Those having experience of leprosy in the African negro will readily realise that Chaussinand's descriptions apply more closely to the disease in Indo-China, as we seldom see the severe lepromatous form depicted, or the neural abscesses described.

The author's own exhaustive researches on the cultivation of the *M.leprae,* as also a review of the literature, justifies his conclusion that the organism has not been grown serially with success. It occurs to us that as the only milieu in which the bacillus does thrive is the human tissue, it seems worth while experimenting with artificial tissue cultures, and as the natural incubation period is two to three years, so the culture should be continued for an adequate length of time, as suggested to us by Turner.

Chaussinand does well to stress that rat leprosy is a different disease to human leprosy, as the rat is refractory to inoculation with the human bacillus, and the geographic distribution of the two maladies do not correspond. The differentiation of the two diseases is further emphasised by the fact that the animal infection is resistant to sulphones, as has recently been demonstrated by Francis.

The clinical description of the disease is both concise and precise, and should be read by those bemused by the various classifications of international conferences. It is unfortunate, however, that the term macule, originally meaning a flat stain of the skin, is used to describe also elevated lesions, originally called plaques. The author is of course appreciative of the distinction, but uses the one term to cover both lesions, because of the common

usage. It is this confusion, or perhaps only a printing error, which led in figure 21, to raised split pea lesions being captioned as macules. The clinician is being severely criticised these days by laboratory workers, independent observers who analyse his results and statisticians, so he should strive after the most exacting precision. The points made in differentiating a tuberculoid case in reaction from the true lepromatous form are well made, but it might have been mentioned that the most reliable criteria are the previous history, and the subsequent course of the malady. This differential diagnosis is most important, as to confuse the two would lead in a clinical trial of a new drug to a false result, as of course the tuberculoid case in reaction tends to a spontaneous subsidence of the lesions.

A most interesting theory on the cross immunisation of leprosy and tuberculosis is described, and supported by arguments so closely made that any fair summary of them is impossible. I venture therefore only a few comments. Chaussinand is of the opinion that the statement of Rogers and Muir that tuberculosis is a common fatal termination of leprosy is too categoric. He holds that it is not true for allergic tuberculoid leprosy which is, on the contrary, resistant to tuberculosis, and records that in 500 tuberculoid cases he found only three with *M.tuberculosis* in the sputum. This argument would be more convincing if post-mortem examinations had been made, a formidable task, and also if the corresponding incidence in lepromatous cases of the same country had been given for comparison. Gehr is quoted as saying that tuberculosis is less prevalent in countries where leprosy is endemic. This does not totally accord with the increase of phthisis in Nigeria. Contrariwise, leprosy is quoted as being rare in countries where tuberculosis is endemic, but the possible causes of the decline of leprosy in Europe are so numerous that it is scarcely justifiable to ascribe it to the rise of tuberculosis. Most authorities will agree with the practical conclusion that B.C.G. vaccination should be more widely applied in countries where both diseases are endemic.

Dr. Chaussinand is to be congratulated for his defence of chaulmoogra therapy, particularly in combination with sulphones, as the present day tendency is to abandon this time honoured remedy. The arguments for the employment of diamino-diphenylsulphone in preference to the more complex preparations are made with clarity. They are (a) that the more complex substances are broken down to the parent sulphone in the body, and thereby exert their action; (b) DADPS can be administered orally; (c) it is cheap and therefore suited to mass therapy. We originaly shared

the enthusiasm of Dr. Chaussinand for an apparently ideal drug, but in our practice using the dosage scheme he describes, it proved too toxic.

Due no doubt to the publication of the monograph last year, no mention is made of the thiosemicarbazones in leprosy, nor to, the relapse rate after apparent cure with sulphones, published by the Carville workers.

We would urge especially physicians in this country to peruse this most readable text, if only because of its style, which never leaves one in doubt as to the author's meaning.

J. BARNES.

Addendum to " Leprosy " (3rd Edition) by Rogers and Muir.

It is a remarkable fact that amongst British Commonwealth workers on leprosy the most outstanding have had long connections with the three Presidency Capitals of India—Calcutta, Madras and Bombay.

In Calcutta Sir Leonard Rogers, the revered and still active doyen of tropical workers, successfully strove in the early part of this century to rescue leprosy from the Slough of Despond, to rationalize its pathology, and to inspire new methods of therapy. His disciples, colleagues and successors, Muir and Lowe, not only carried on the good work in Calcutta, but have since had wide experience in the West Indies and in tropical Africa. Muir, who recently returned to the U.K., enriched with new experience in the Purulia Leprosarium, in Bihar, has now collaborated with Sir Leonard in the production of a much needed therapeutic " addendum " to their standard work on leprosy.

The advent of the sulphones has apparently improved our powers of affording relief to sufferers from leprosy. It is, however, particularly necessary to remind ourselves that leprosy is a disease to be prevented or treated; a scientific problem to be approached in a cool, detached and critical spirit; not a cause to be won!

The somewhat over-optimistic reports on the curative powers of chaulmoogra derivatives in certain forms of leprosy led to premature " Leprosy can be cured " propaganda twenty years ago, with subsequent disillusionment. We must be most careful not to let history repeat itself and to " play down " the sulphones and newer remedies till they are thoroughly tried and understood. This is especially necessary as invasion of the body by *M.leprae*, is apparently resisted by a high proportion of human beings, whilst many others cope successfully with the bacilli after invasion, without developing clinical signs of the disease. A number of those who

develop clinically demonstrable lesions do so temporarily and cure themselves spontaneously; the remainder fight long battles with the bacilli and eventually win through at a terrible price of suffering and mutilation.

Safe and successful therapy must encourage the gradual destruction of the bacilli and their products without killing too many too quickly, with resulting severe reactions, nerve strangulation and agonizing pain.

It cannot be said that any safe, reliable standard sulphone therapy has yet been worked out.

Even with the small number of active cases at the Jordan Hospital, the leprosy unit at Redhill, four forms of sulphone therapy are at present on trial. With one major lepra reaction from DDS, one moderately severe reaction from thiosemicarbazone, and a case of retrobulbar neuritis from the same drug, it is obvious that we have much to learn.

On general principles it is better to be safe than sorry. Earlier workers tended to give sulphones in too high dosage. Some workers would not agree with Rogers and Muir that " there is a considerable space between the minimum effective dose and the maximum subtoxic dose." The suggested daily dose of 4 mg. per kilo of body weight would by some be regarded as high.

The inexperienced worker will " ca' canny " with the sulphones, starting with small doses and gradually working up towards the higher recommended dosage as his experience increases.

The ' Calcutta School ' are to be congratulated on the prompt production of this inexpensive but comprehensive and thought-provoking " addendum." Lowe's fine work in Africa is, naturally, commended. It would have been a gracious act if some reference had been made to one described by Lowe as " the father of DDS therapy "—R. G. Cochrane, whose introduction of an injectable DDS and of sulphetrone as a watery solution for parenteral use has had a powerful influence on sulphone therapy, and whose fine researches on skin and nerve pathology inspired Khanolkar's most important recent researches in Bombay.

GEORGE R. MCROBERT.

International Journal of Leprosy, Vol. 18, 2, (April-June, 1950).

Organization of the Anti-Leprosy Campaign in Madagascar, by Grimes, C. A full account of the development and present status of leprosy activities in Madagascar, by the medical officer in charge of the Leprosy Service.

Laws and Regulations relating to Leprosy in the United States of

America, by Doull, J. A. The title of this article is an indication of its scope and contents, and should be consulted in the original by those interested.

Lipoids in the Reactional Tuberculoid Leprosy Granuloma, by Campos, R. de C. J. The author has studied the question of the presence of lipoids in leprous granulomas by means of staining frozen sections of skin with Sudan IV. He found that cells of the granulomatous lesions of almost all lepromatous and reactional tuberculoid cases contained lipoid material, whereas the granuloma of the ordinary tuberculoid was wholly lacking in lipoid. The value of this observation in the differential diagnosis of lepromatous and tuberculoid leprosy is discussed.

An Acid-fast Microorganism cultivated from Leprous Material. Bacteriological and Serological Observations by Terni, M. and Signorini,, F. L. Attempts were made to cultivate the leprosy bacillus on Dubos' medium, and the larvæ of the wax method of *Galleria mellonella* (an insect very susceptible to tuberculosis infection.) All attempts failed except one, and this one was a skin leproma inoculated into a larvæ and then into Petrognani's medium. Three months later a colony of acid-fast gram-positive bacteria, aerobic, nonencapsulated, nonspore-forming and non-motile were observed. Optimum growth was obtained at 37° C. Complement-fixation tests and attempts to lyse the organism by macrophages led the authors to conclude that the bacteria were more like those of *M.leprae*, than *M.tuberculosis.*

Evaluation of the Cardioliphin Antigen in the Tests for Syphilis in Leprosy. By Shively, J. A. and Kuhns, D. M. The cardiolipin antigen was shown to reduce significantly the number of false positives obtained in the serological test for syphilis in patients suffering from leprosy. False positives with the cardiolipin complement-fixation test were obtained in 31 out of 120 known syphilitic patients, compared with 63 Kahn positives and 59 Kolmer positives.

Allergie et Para-Allergie dans la Lepre. By Floch, H. and Destombes, P. The authors suggest that results obtained by lepromin testing indigenous and non-indigenous inhabitants of French Guiana, confirm the theory of relative immunity developed by indigenous inhabitants of French Guiana (as opposed to the relative non-immunity of Europeans resident there). They consider the results of lepromin tests in endemic and non-endemic areas, and disagree with the conclusion of Dubois that a positive reaction in

a person in a non-endemic country is caused by a local irritant action of the body towards the bacilli. They consider that a positive test in a non-contact is due to a para-allergy developed by the use of other acid-fast organisms. Results of tuberculin tests in infants and children are given, and comparison is made with the results of lepromin tests carried out at the same time. From their studies the authors conclude that the tubercle bacillus is capable of producing a state of para-allergy to the leprosy bacillus. They have now commenced a study of the effect of B.C.G. vaccination on negative reactors to lepromin, in an attempt to produce a state of positive para-allergy.

The Tissue Sites most favourable for the Development of Murine Leprosy in Rats and Mice. By Hanks, J. H. and Backerman, T. The authors attempted to discover the tissues and organs in which the most rapid development of *M. leprae murium* occurs. Known numbers of bacilli obtained from clarified supernatants of bacillary emulsions were used for inoculation. Inoculations were made in the anterior chamber of the eye, the brain, the peritoneum, the dermis and epidermis and the testes. The results presented are of a highly technical nature and those interested in this aspect of leprosy should consult them in the original. Using the Hawaiian strain of *M. leprae murium*, it was discovered that the Wistar strain of rats are relatively resistant to infection. Intraperitoneal inoculation of these rats did not produce a progressive infection of the omentum, mesenteries, lymph nodes, spleen, etc., and thus this leprosy conforms more closely to the human than usual. The testes proved to be the organ from which the greatest number of bacilli could be recovered, and in which the greatest lesions were produced.

The Mitsuda Reaction in a Non-Leprous Area. By Rotberg, A. Bechelli, L. M. and Keil, H. The authors examine the question of lepromin positive non-contacts. They study the lepromin and tuberculin reaction in non-contacts in non-endemic areas, and in non-contacts in endemic areas. Using lepromin and tuberculin they cross tested each of the above groups. 18 per cent of non-contacts in non-endemic areas were lepromin positive—this figure was approximately the same for both healthy cases and active tuberculoid cases. In an endemic area the percentage of positives in non-contacts was 54 per cent. 13 per cent of non-contacts in a non-endemic area were both lepromin and tuberculin negative, whilst 18 per cent were strongly tuberculin positive and lepromin negative. These figures would seem to disprove the para-allergy theory of

Floch and Destombes, mentioned elsewhere in this Journal. The authors suggest that the explanation of the phenomenon of tuberculin positive, lepromin negative, cases, is that cross sensitization is not obligatory. The matter is left very much in doubt by the authors, who conclude that if the cross sensitization theory is not satisfactory or possible in any other way, it will be necessary to search for other factors to explain the positive lepromin reactions in non-endemic countries. This careful article is well worth a detailed study.

Promacetin in Treatment of Leprosy. Progress Report. by Johansen, F.A. et al. Promacetin, the latest of the sulphones, is basically DDS, orthosubstituted with a single sulphonamide grouping. It possesses two free amino groups. It is active in streptococal infections in mice, and in pneumococcus pneumonia in man. It is not active against tuberculosis in guinea pigs. 27 patients were treated with this drug; 23 were lepromatous, one tuberculoid. 17 patients had received no previous treatment. Two had had chaulmoogra oil and 8 sulphones. No serious toxic effects were observed, and the cases responded kindly to treatment. A significant fact was that patients (treated with other sulphones previously) having stationary residual lesions, showed renewed clearing up on promacetin therapy. The authors suggest that wider application should be made of alternating sulphones in the treatment of leprosy. The article also raises the interesting point that promacetin, which fails to protect the guinea pig against tuberculosis, is apparently effective in another acid-fast infection, i.e. leprosy. This raises the pertinent question as to whether drugs of possible value in the treatment of leprosy, should be found by experimental screening methods used, as at present, in experimental tuberculosis in animals.

M. SMITH.

Four Years Experience of Sulphone Treatment of Leprosy. By Lowe, J. and Davey, T. F. (Trans. Roy Soc. Trop. Med. Vol, 44, No. 6. June, 1951.)

The authors present the results as a whole of 4 years sulphone treatment of leprosy. Experience has been confined to diasone, sulphetrone (orally) and DDS (called DADPS in the article).

Diasone was used in 40 cases for 18 months, and in 20 for a further few months, but treatment with this drug finally ceased because of currency difficulties.

Sulphetrone was used in 260 cases for periods varying up to

3½ years. DDS has been used in 400 cases for periods up to 21 months, and has now been adopted for routine treatment. The dosage of DDS used has been standardised at 200 mg. a day, given after a preliminary course of 6 weeks on 100 mg. With all sulphone therapy freshly prepared ferrous sulphate has been given routinely to combat anaemia.

The authors go on to discuss the pharmacology of the sulphones and suggest that DDS is the active principle of the proprietary sulphones, and can produce the same effect in small doses as the larger doses of the complex sulphones.

Toxic effects are given as follows:—(a) *Anaemia*, for which iron only is necessary. (b) *Dermatitis* occurred in 2% of patients: if sulphone treatment is not stopped this dermatitis may proceed to exfoliation or death. Dermatitis was recorded as rare in female patients. Dermatitis always occurs during the first six weeks of treatment, or not at all, and if a relatively low dose is maintained during the initial 6 weeks of treatment, the occurrence of dermatitis may be prevented and its incidence considerably reduced. Instructions are given regarding the desensitization of patients who have become allergic to sulphones. *Sulphone psychosis* was observed in 6 of 350 cases being treated with DDS, but no cases were observed in 200 other cases being treated elsewhere. *Reaction*—erythema nodosum—is not considered to be a toxic effect of the sulphones, but an effect of the sulphones upon the bacillus. It is not considered that this condition is of bad prognostic import. Anti-histamine drugs were found of little value in this condition, but in the neuritis that accompanies reaction they are sometimes of value. Antimony compound is of value in controlling the reaction. *Glandular fever.* The administration of sulphones can precipitate an attack of glandular fever, presumably in a person with a latent infection.

Clinically the response to treatment is the same as that now generally accepted. Bacteriologically, six tables are presented to show the results of treatment. The group started in 1946, having had diasone, then sulphetrone, and then DDS treatment for a period of 40-48 months, records a negative rate of 80%. Another group treated only with sulphetrone for 30-38 months records a 40% negative rate. A third group treated mainly with sulphetrone for 24-30 months shows a 40% negative rate. A fourth group, having had 12-24 months with sulphetrone and then 5 months with DDS, shows a negative rate of 28%. Group E, after 12-18 months treatment with DDS, shows a 24% negative rate.

In the discussion of results the authors bring out two main points: (1) the constancy of response, and (2) the slowness of

response. With regard to (1) it is stated that improvement occurred in every case treated, and that in no case was it found impossible to use the sulphones; and with regard to (2) it is stated that the time necessary to render cases inactive and negative is directly proportional to the severity of the infection. 1+ cases usually take 1 year, 2+ cases 2—3 years, 3+ cases 3-4 years, and 4+ cases 4—5 years. The suggestion is made that the long time necessary for dead *M. leprae* to disintegrate in the tissues is one factor which has to be considered when the bacteriological slowness of response is in question. In tuberculoid cases response is much faster, clinical changes being occasionally demonstrable within 1 week. Skin lesions subside rapidly, nerve lesions more slowly. It is considered that the sulphone treatment of tuberculoid leprosy is highly satisfactory

DDS is considered to be the sulphone of choice, and has now been adopted as the standard treatment in Nigeria and elsewhere.

The authors report their results on blood and skin levels of DDS, and go on to discuss the value of DDS treatment in various types of cases.

A later note to the article gives the authors' views a year later. Twice weekly treatment is better tolerated and no less effective than daily treatment. 400 mg. twice weekly is suggested as the dose, and with this regimen the incidence and severity of toxic effects are considerably reduced. Iron treatment may be omitted in well nourished patients since the anaemia is unusual. The authors have shown that the administration of complex sulphones by mouth produces a therapeutic blood level of DDS. 20,000 cases are now under treatment in many widely scattered centres.

Of 139 lepromatous cases discharged, no clinical relapses have been seen; two showed scanty bacilli on bacteriological examination, and both cases became negative again within a few months of re-starting treatment.

Attempts have been made to speed up treatment by combining DDS with other chemotherapeutic agents. *Streptomycin* has a rapid therapeutic effect in tuberculoid cases, when given in short courses either alone or in combination with DDS. *Thiacetazone* is giving promising results, but it cannot be used with DDS. *P.A.S.* is much less active than DDS, thiacetazone or streptomycin.

M. SMITH.